

Correlation between Nerve Growth Factor (NGF) with Brain Derived Neurotrophic Factor (BDNF) in Ischemic Stroke Patient

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Background: The neurotrophins nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) is a family of polypeptides that play critical role during neuronal development, appear to mediate protective role on neurorepair in ischemic stroke. Naturally in adult brain neurorepair process consist of: angiogenesis, neurogenesis, and neuronal plasticity, it can also be stimulated by endogenous neurorepair. In this study we observed correlation between NGF and BDNF ischemic stroke patient's onset: 7-30 and over 30 days. **Methods:** This is cross sectional study on 46 subjects aged 38 – 74 years old with ischemic stroke from The Indonesian Central Hospital of Army Gatot Subroto Jakarta. Diagnosis of ischemic stroke was made using clinical examination and magnetic resonance imaging (MRI) by neurologist. Subjects were divided into 2 groups based on stroke onset: 7 – 30 days (Group A: 19 subjects) and > 30 days (Group B: 27 Subjects). Serum NGF levels were measured with ELISA method and BDNF levels were measured using multiplex method with *Luminex Magpix*. **Results:** Levels of NGF and BDNF were significantly different between onset group A and B (NGF $p=0.022$, and BDNF $p=0.008$), with mean levels NGF in group A higher than group B, indicating that BDNF levels is lower in group A than group B. There was no significant correlation between NGF and BDNF levels in all groups. **Conclusion:** The variations in neurotrophic factor levels reflect an endogenous attempt at neuroprotection against biochemical and molecular changes after ischemic stroke. NGF represents an early marker of brain injury while BDNF recovery is most prominent during the first 14 days after onsite but continuous for more than 30 days. There is no significant correlation between NGF and BDNF in each group.

Keywords: Ischemic Stroke, NGF, BDNF

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INTRODUCTION

Stroke is one of the biggest neurological threats that causes disability in patient. Epidemiological studies in developing countries showed significantly increased incident in 20 years.¹ Efforts to develop therapeutic strategies that are applied after an ischemic stroke for triggering recovery of function and stimulate neural plasticity (neuroplasticity) are applied in conjunction with neurorehabilitation (neurorepair).²

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Several stroke studies indicate increased levels of neurotrophic growth factors have a protective role.³ Neurotrophic factors are endogenous molecules play a role in repair-regeneration process such as axonal regeneration, neurogenesis, and neuronal plasticity, in fact protection against degeneration and lesions, that could be critical for recovery after ischemic stroke. The family of neurotrophins includes Nerve growth factor (NGF) and Brain-derived neurotrophic factor (BDNF).⁴

NGF is a neurotrophic that support the survival and differentiation of neurons⁵, lowering the degeneration of nerve, and triggers nerve regeneration.⁶ NGF is critical to the survival and maintenance of neuron after cerebral hypoxia-ischemia.⁷

BDNF is member of a neuronal growth factor is the most widely neurotrophins excreted in the central nervous system mature. BDNF works through high affinity cell surface receptors (TrkB).⁸ Maintaining the viability of the various types of neurons and prevent neuronal death after cerebral ischemia by activating intracellular protein kinase B, MAPKs and ERKs.⁹

The aim of this study is to observe the correlation between NGF and BDNF in patients with ischemic stroke with difference onset time.

MATERIALS AND METHODS

This is a cross-sectional study with 30 – 60 years old ischemic stroke subjects from The Central Hospital of the Army (RSPAD) Gatot Subroto Jakarta. Diagnosis of ischemic stroke were determined by clinical examination and MRI.

Subjects were divided into 2 groups based on onset time of stroke. Group A are patient with onset 7 – 30 days and Group B are patient with onset more than 30 days. Subject with a history of carcinoma, hematoma subdural, or other carcinoma, global ischemia, seizures, blood clotting disorders, and could not conduct MRI were excluded.

Specimen collection

Blood were collected intravenously, serum was generated, stored frozen (at -21°C), and tested for biomarkers. NGF concentrations were measured using ELISA method and BDNF concentrations were measured using multiplex method (Reagent R&D no cat LXSAHM-03) with *Luminex Magpix* instrument

Statistical analysis

Statistical analysis was performed using SPSS for Mac version 20 for normal distribution was analyzed by Kolmogorov Smirnov and difference significance for each groups was analyzed by t-test analysis. Meanwhile correlation of NGF with BDNF analyzed by Pearson analysis.

RESULT

We used 46 ischemic stroke subjects, which divided onto 2 groups of: 19 subjects for group A, 27 subjects for group B. Characteristics of subjects and the results of normality test data are shown in Table 1.

Table 1. General characteristics of subjects and normality test (n=46)

Variable	Min	Max	Mean ± SD	Median	p
Age (years)	38	74	56.9 ± 9.43	56	0.658*
BMI (kg/m ²)	16.6	31.7	24.6 ± 3.21	23.5	0.160*
SBP (mmHg)	57	120	86 ± 13	85	0.223*
DBP (mmHg)	106	220	146 ± 25	140	0.311*
BDNF (pg/ml)	6,105	33,967	18,889 ± 6,105	18,320	0.983*
NGF (pg/ml)	4.35	9.67	5.89 ± 0.81	5.75	0.244*

*Distribution assessment with Kolmogorov Smirnov test, BMI: Body Mass Index

Differences BDNF and NGF levels on onset stroke

We found Levels of NGF and BDNF in table 2 significantly different between onset group A and B (NGF p= 0.022, and BDNF p=0.008). We also found mean levels NGF in group A higher than

group B whereas mean BDNF levels appear lower in group A than group B. There is no significant difference for variables age, BMI, Systolic, and Diastolic between the groups onset.

Table 2. Comparison of biomarkers among groups

Variable	Subjects Onset Group		Independent t-test p
	7 - 30 days after onset (n=19)	>30 days after onset (n=27)	
Age (years)	58 ± 10.52	56 ± 8.7	0.503
BMI (kg/m ²)	24.7 ± 3.1	24.1 ± 3.4	0.768
SBP (mmHg)	88 ± 16.9	83 ± 9.6	0.224
DBP (mmHg)	145 ± 30	147 ± 20	0.856
BDNF (pg/ml)	15,777 ± 5,476	21,097 ± 6,962	0.008*
NGF (pg/ml)	6.21 ± 1.0	5.66 ± 0.54	0.022*

* Significantly independent t-test p<0.005

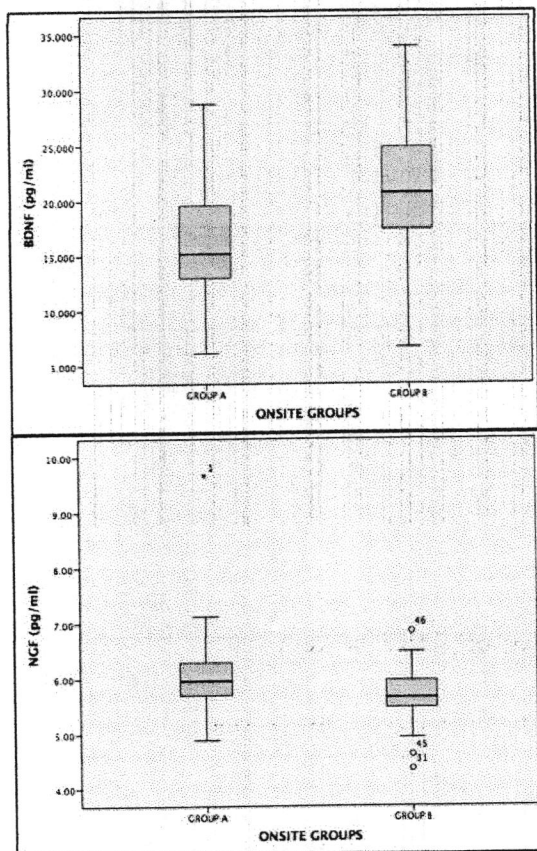


Figure 1.
Comparison mean of BDNF and NGF among groups

Correlation between BDNF and NGF

Using Pearson correlation test, no such significant correlation was found between NGF and BDNF concentration in each subject group

Table 3. Correlation analysis Between BDNF and NGF

Group Onset	p	r
A (n=19)	0.388	0.233
B (n=27)	0.456	- 0.150

DISCUSSIONS

Levels of NGF and BDNF significantly different between onset group A and B, with mean levels NGF in group A higher than group B. whereas mean BDNF levels appear lower in group A than group B. During and immediately after stroke, neurological functions recovery is most prominent during the first 30 days.¹⁰ The describe of NGF levels between group similar with results study T H Lee et al, in the peri-infarct penumbra area, despite a decrease in NGF at hour 4 and day 1, NGF recovered beginning at day 3 and returned almost to the sham-control level at day 14. In the non-

ischemic cortex, NGF increased beginning at hour 4, peaked at day 7, and returned almost to the sham control level at day 14.¹¹

After brain damage due to hypoxic ischemia, elevated expression of NGF plays a key role in the response after the injury, and may have a beneficial impact on the regenerative capacity of the injured tissues.¹² The action of NGF in modulating the cerebral tissue viability might be due to the role exerted by NGF in favoring the biosynthesis of doublecortin (DCX), a protein expressed by new neurons after brain stroke.¹³ Recent studies find neuroprotective role of others neurotrophins. BDNF is up-regulated at very early stages during brain ischemia, suggesting endogenous neuroprotective mechanisms in viable neuronal networks.¹⁴

BDNF levels were significant difference between group A and B, with mean levels BDNF level in group A lower than group B. Animal study reported that BDNF secreted by human bone marrow-derived MSCs (hBMSCs) was upregulated at 7 days and significantly increase expression at 14 days (15). The following process on survival neuron and proliferation parenchymal cell increase plasticity after 2-3 weeks.¹⁶ BDNF induced Microtubule-Associated Protein 1B (MAP1B) expression in the ischemic border zone and synaptophysin expression within the contralateral cortex 6 weeks after ischemia.¹⁷

CONCLUSIONS

The variations in neurotrophic factor levels reflect an endogenous attempt at neuroprotection against biochemical and molecular changes after ischemic stroke. NGF represents an early marker of brain injury while BDNF recovery is most prominent during the first 14 days after onsite but continues for more than 30 days. There is no significant correlation between NGF and BDNF in each group.

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